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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/623,922

08/31/2001

Vassilios Papadopoulos

1941.017US1

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07/02/2007

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.

P.O. BOX 2938

MINNEAPOLIS, MN 55402

EXAMINER

DANG, IAN D

ART UNIT

PAPER NUMBER

1647

MAIL DATE

DELIVERY MODE

07/02/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/623,922	Applicant(s) PAPADOPOULOS ET AL.	
	Examiner Ian Dang	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 and 32-38 is/are pending in the application.
- 4a) Of the above claim(s) 9-19, 21-30 and 32-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-30 and 32-38 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/31/2006, 4/25/2007</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Exhibit A</u> . |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-8 and 20 in the communication filed on 01/25/2007 and 31 July 2006 is acknowledged. Applicant has further elected with traverse the species SEQ ID NO:5 in communication filed 04/25/2007. The traversal is on the ground that the species are structurally similar and the sequences subject to the species election have a cholesterol recognition/interaction sequence, and so form a single general inventive concept.

Applicant's arguments of 25 April 2007 regarding the traversal of the election of the species SEQ ID NO:5 have been fully considered but are not found persuasive. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant's arguments of 31 July 2006 regarding the traversal for the election of Group I have been fully considered but are not found persuasive. The inventions listed as Groups I-XII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Art Unit: 1647

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as Groups I-XII do not relate to a single general inventive concept because they lack the same or corresponding technical feature.

Claim 1 is directed to a consensus sequence VLNYYNWR (SEQ ID NO:5) of peripheral-type benzodiazepine receptor (PBR). Garnier et al. (1994, Molecular Pharmacology, Volume 45, pages 201-211) teach the consensus sequence VLNYVWR (Figure 1, page 204, amino acid residues 149-156) that is 100% identical to the cholesterol recognition/interaction amino acid consensus sequence SEQ ID NO: 26 meeting the limitations of claim 1. The prior art meets the limitations disclosed in claim 1. Thus Group I lacks novelty or inventive step and does not make a contribution over the prior art. Since the first claimed invention has no special technical feature, it cannot share a special technical feature with the other claimed invention.

Under PCR Rule 13.1, the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

The requirement is still deemed proper and is therefore made FINAL.

Claims 9-19, 21-30, and 32-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 31 July 2006.

Claims 1-8 and 20 are pending and under examination.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/077,753 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The claimed invention drawn to a cholesterol recognition/interaction amino acid consensus comprising SEQ ID NO:5. The amino acid sequence of the SEQ ID NO:5 is not disclosed in the U.S. provisional application 60/077,753 but is disclosed in the PCT application US/99/05853 filed on 03/12/1999. Therefore, the instant application gets the priority of the U.S. application 09/623,922 filing date of 08/31/1999.

Information disclosure statement

The information disclosure statement filed 10/31/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The references were unable to located and hence have not been considered by the Examiner. Please submit a courtesy copy of the references and a new PTO-1449.

Claim Rejections - 35 USC § 101-non-statutory subject matter

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 and 20 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

The claims read on the presence of the cholesterol recognition/interaction amino acid consensus inside a cell or an animal. Claims read on a product of nature in that the claimed cholesterol recognition/interaction are not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980).

Claim Rejections - 35 USC § 112 (Written Description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and claim 20 is drawn to a peptide comprising a cholesterol interaction/recognition sequence.

Art Unit: 1647

The Examiner has broadly interpreted claim 20 as reading upon any variants, derivatives, and fragments of a cholesterol recognition/interaction consensus and an infinite number of large protein sequences that comprise such. Specifically the specification teaches that it would be within the skill of a person with ordinary skill in the art to design mutant proteins in which the cholesterol recognition/interaction consensus sequence has been altered such the protein's ability to interact/recognize cholesterol is reduced, increased, or abolished. (page 13 lines 17-24).

Thus, the claims are genus claims. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Specifically, the specification does not clearly define a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and a peptide comprising any variants, derivatives, and fragments of a cholesterol interaction/recognition sequence. Thus, the scope of the claims includes numerous structural and functional variants, and the genus' are highly variant because a significant number of structural and functional differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural and functional features that could distinguish a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and a peptide comprising any variants, derivatives, and fragments of a cholesterol interaction/recognition sequence from other cholesterol recognition/interaction amino acid consensus sequences comprising SEQ ID NO:26 and other peptides comprising any variants, derivatives, and fragments of a cholesterol interaction/recognition sequence are missing from the disclosure. No common attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify

Art Unit: 1647

members of the genus, and because the genus is highly variant, a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and a peptide comprising any cholesterol recognition/interaction amino acid consensus sequence of SEQ ID NO:26 or variants, derivatives, and fragments of such are insufficient to describe the genus.

The written description requirement for a claimed genus' may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus for a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and a peptide comprising any cholesterol recognition/interaction amino acid consensus sequence of SEQ ID NO:26 or variants, derivatives, and fragments of such.

There is no description of the special features, which are critical to the structure and function of the genus claimed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and a peptide comprising any cholesterol recognition/interaction amino acid consensus sequence of SEQ ID NO:26 or variants, derivatives, and fragments of a cholesterol interaction/recognition sequence encompassed by the limitations. Thus, no identifying characteristics or properties of the claimed a cholesterol recognition/interaction amino acid

Art Unit: 1647

consensus sequence comprising SEQ ID NO:26 and a peptide comprising any cholesterol recognition/interaction amino acid consensus sequence of SEQ ID NO:26 or variants, derivatives, and fragments of such are provided such that one of skill would be able to predictably identify the encompassed variant biological and chemical entities recited in the instant claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 1-8 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated consensus sequence consisting of VLNYYNWR (SEQ ID NO:5) of peripheral-type benzodiazepine receptor (PBR) does not reasonably provide enablement for a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and any peptide comprising a cholesterol interaction/recognition sequence encoded by SEQ ID NO:26. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breadth of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

Nature of the invention and breath of the claims

The invention is drawn to the cholesterol recognition/interaction amino acid consensus sequence VLNYYNWR (SEQ ID NO:5) of the peripheral-type benzodiazepine receptor (PBR) polypeptide. The invention is broad because the recitation of claims 1-8 and 20 encompasses a large number of polypeptides. Specifically, the specification teaches that that the cholesterol recognition amino acid sequence on PBR is common to all proteins shown to interact with cholesterol (page 3, lines 17-20).

Unpredictability and state of the art

The state of the art for the cholesterol recognition/interaction amino acid consensus sequence VLNYYNWR (SEQ ID NO:5) of the peripheral-type benzodiazepine receptor (PBR) polypeptide is well established, but the cholesterol recognition/interaction amino acid consensus sequence of SEQ ID NO:26 and any polypeptide comprising the recognition/interaction amino acid consensus sequence of SEQ ID NO:26 are not well characterized.

The instant cholesterol recognition/interaction amino acid consensus sequence for PBR has been characterized in the specification and in several references. For instance, Lacapere et al. (2003, Steroids, Volume 68, pages 569-585) recite that the characterization of the consensus sequence is well characterized for PBR and been identified for other proteins. For instance, Lacapere et al. teach that the deletion of the C-terminus of PBR (delta 153-169) drastically reduced cholesterol uptake (70%), although it retained ability to bind PK 11195 ligand. Site directed mutagenesis in this 153-169 region enabled the characterization of amino acids involved in cholesterol binding. A CRAC sequence has been determined (ATVLNYYVWRDNS) and this amino consensus pattern has been observed in several other proteins known to interact with cholesterol (page 577, right column, 2nd paragraph).

Although the cholesterol recognition/interaction amino acid consensus sequence for PBR is characterized, the functional activity of how PBR transports cholesterol is presently under investigation. For instance, Jamin et al. (2005, *Molecular Endocrinology*, Volume 19, pages 588-594) teach that although the role of PBR in cholesterol transport across the outer mitochondrial membrane has been shown in various steroid and bile producing tissue, the exact role mechanisms by which protein binds and translocates cholesterol remains poorly understood (page 591, right column, 1st paragraph of discussion).

In addition, the cholesterol recognition/interaction amino acid consensus sequence is present in numerous proteins, but its activity regarding the recognition and interaction with cholesterol in other proteins besides PBR has not been determined. For example, Li et al. (1998, *Endocrinology*, Volume 139, pages 4991-4997) teach that given any tyrosine there is a reasonably high probability that this consensus will be found in many proteins. Indeed a motif search through the various gene data banks indicated that this amino acid consensus pattern is present in various proteins (page 4995, right column, last paragraph). However, the biological significance for the presence of the consensus in numerous proteins has not been determined at this point. For instance, Li et al. (1998) recite that it is possible that only in some proteins this consensus sequence will be functional (page 4996, left column, top paragraph). Moreover, Li et al. (1998) teach that the strength and specificity of the interaction of a protein containing this consensus amino acid sequence with cholesterol may be due to either the presence of a certain microenvironment, or the location of the consensus sequence within the protein, or a specific conformation of the protein that allows the use of this amino acid sequence (page 4996, left column, top paragraph).

In view of these teachings in the art and the limited guidance provided in the specification, the cholesterol recognition/interaction amino acid consensus sequence consisting

Art Unit: 1647

of VLNYYNWR (SEQ ID NO:5) of the peripheral-type benzodiazepine receptor (PBR) polypeptide is not predictable for a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and any peptide comprising a cholesterol interaction/recognition sequence encoded by SEQ ID NO:26.

The amount of direction or guidance present

Applicants' disclosure is limited to cholesterol recognition/interaction amino acid consensus sequence VLNYYNWR (SEQ ID NO:5) of the peripheral-type benzodiazepine receptor (PBR) polypeptide. The specification provides numerous examples (Figures 1, 3, and 4) and recites that the carboxy terminal of PBR is responsible for the interaction and subsequent uptake of cholesterol.

Although the specification teaches that it would be within the skill of a person with ordinary skill in the art to design mutant proteins in which the cholesterol recognition/interaction consensus sequence has been altered such the protein's ability to interact/recognize cholesterol is reduced, increased, or abolished. (page 13 lines 17-24), the specification does provide any specific guidance for any variants, derivatives, and fragments of a cholesterol recognition/interaction consensus encompassing an infinite number of large protein sequences.

However, the specification does not provide any guidance or direction regarding the biological functions of the cholesterol recognition/interaction consensus sequence of other polypeptides. While the teachings of the cholesterol consensus applies to PBR, these specificities and biological activities for the cholesterol recognition/interaction amino acid consensus of PBR may not be applicable to proteins disclosed in Table 1 (page 12). The specification recites that the presence of the cholesterol interaction/recognition consensus sequence in the proteins listed in table 1 signifies the likelihood that the proteins interact with

Art Unit: 1647

cholesterol and provides insight into how these proteins accomplish their functions in concert with cholesterol and how to alter these functions (page 13, lines 1-7).

Working Examples

Although Applicants have provided several examples for the characterization of the biological activity for the cholesterol sequence consensus of PBR, the specification does not provide any working examples for the biological activity for the consensus sequence of other proteins. Specifically, the examples in the specification disclose that PBR ligands induce the transport of cholesterol and pregnenolone formation (Figure 1), PBR expressed in bacteria transports radioactively labeled cholesterol (Figure 3), several proteins include the a cholesterol recognition/interaction amino acid consensus pattern Table 1 (page 12). However, there are no examples disclosing the biological activities of other proteins having the consensus sequence.

The quantity of experimentation needed

Without sufficient disclosure in the specification, it would require undue experimentation for one of skill in the art to make/use the a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and any peptide comprising a cholesterol interaction/recognition sequence encoded by SEQ ID NO:26. In addition, it would require undue experimentation to practice the invention commensurate in scope with the claims because, the claims are broadly drawn to a cholesterol recognition/interaction amino acid consensus sequence comprising SEQ ID NO:26 and any peptide comprising a cholesterol interaction/recognition sequence encoded by SEQ ID NO:26.

Art Unit: 1647

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Garnier et al. (1994, Molecular Pharmacology, Volume 45, pages 201-211).

Garnier et al. (1994) teach the consensus sequence VLNYYVWR that is 100% identical to the cholesterol recognition/interaction amino acid consensus sequence SEQ ID NO: 5 meeting the limitations of claim 1. Moreover, Garnier et al. recite that the consensus sequence includes the amino acid residue Z as a leucine, Y as a tyrosine, and Q as an arginine meeting the limitations of claims 2-5. In addition, Garnier teach that X is two amino acids meeting the limitations of claims 7-8. The consensus sequence is present from amino acid residues 149 to 156 of the benzodiazepine receptor polypeptide (see alignment in Exhibit A) meeting the limitations of claims 1-8 and 20.

Conclusion

No claim is allowed.

Information

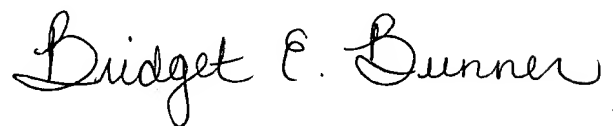
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

Art Unit: 1647

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
June 19, 2007

A handwritten signature in cursive script that reads "Bridget E. Bunner".

**BRIDGET BUNNER
PATENT EXAMINER**

<!--StartFragment-->

RESULT 1

I57953

peripheral-type benzodiazepine receptor - mouse

C;Species: Mus musculus (house mouse)

C;Date: 02-Aug-1996 #sequence_revision 02-Aug-1996 #text_change 12-Jul-2004

C;Accession: I57953

R;Garnier, M.; Dimchev, A.B.; Boujrad, N.; Price, J.M.; Musto, N.A.; Papadopoulos, V.
Mol. Pharmacol. 45, 201-211, 1994

A;Title: In vitro reconstitution of a functional peripheral-type benzodiazepine recept

A;Reference number: I57953; MUID:94158796; PMID:8114671

A;Accession: I57953

A;Status: preliminary; translated from GB/EMBL/DDBJ

A;Molecule type: mRNA

A;Residues: 1-169 <RES>

A;Cross-references: UNIPROT:P50637; UNIPARC:UPI0000001139; GB:L17306; NID:g309441; PID
C;Superfamily: peripheral-type benzodiazepine receptor/signal transduction protein Tsp

Query Match 100.0%; Score 48; DB 2; Length 169;

Best Local Similarity 100.0%; Pred. No. 0.17;

Matches 8; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 VLNYVWR 8

|||||||

Db 149 VLNYVWR 156

Application 09/623,922

<!--EndFragment-->

Exhibit A